50.4%) than non-PAD subjects ($P < .001$). PAD subjects were more likely to have CAS (17.5% vs 3.4%), prior strokes (5.4% vs 1.6%), prior transient ischemic attack (8.1% vs 3.2%), prior myocardial infarction (10.3% vs 3.6%), and prior coronary revascularization (14.8% vs 4.9%) than non-PAD subjects ($P < .001$). There was a statistically significant correlation between decreasing ABI value and an increased prevalence of CAS, CAD, and CVD ($P < .001$) (Fig). For example, patients with an ABI between 0.41 and 0.60 had a 26.4% incidence of CAS, which increased to 34.9% for those with an ABI ≤ 0.4. Even patients with a minimally decreased ABI (0.81-0.9) had significantly increased rates of vascular disease in other territories compared with patients with normal ABIs.

Conclusions: The ABI value is directly and significantly associated with the prevalence of CAS, and with a history of CAD and CVD complications. These data support the use of the ABI as a noninvasive, inexpensive, easily reproducible screening test that can reliably identify patients at increased risk for cerebrovascular and cardiovascular complications.

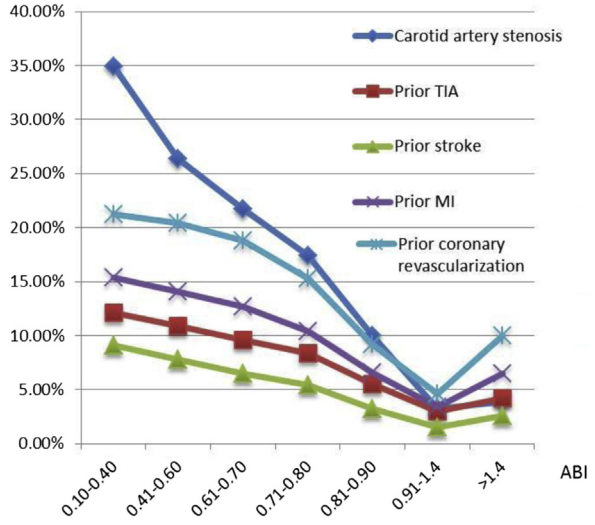

Fig.

A Systems Based Analysis of p27kip1 as the Driver for Pathologic Vein Graft Remodeling

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Objectives: The factors that lead to vein graft bypass restenosis and ultimate clinical failure are incompletely understood. Cell cycle regulators, such as the cyclin-dependent kinase inhibitor $p27^{kip1}$, have been shown to play critical roles in the regulation of vascular cell proliferation. Conte et al and van Tiel et al, in fact, have identified a single nucleotide polymorphism (SNP) in the promoter region of the $p27^{kip1}$ gene that is associated with divergent clinical outcomes following lower extremity vein bypass grafting and coronary artery stenting, respectively. Both clinical studies demonstrated the $p27^{kip1}$-838C>A SNP to be associated with significantly increased rates of clinical success compared with the -838CC and -838CA genotypes. Although these represent highly significant and clinically relevant findings, these studies are primarily associative in nature and provide limited insight into the mechanistic details. Here we aim to develop a model to explore the precise mechanisms through which $p27^{kip1}$ influences the local vascular wall biology. There is a long history of divergent phenotypes of vein graft remodeling secondary to alterations in flow and wall shear stress. Previous work in our laboratory using a novel vein graft model demonstrated increased outward remodeling and decreased neointimal hyperplasia in response to high-shear environments. Using high-throughput genomics, we examined the specific genes and pathways that are closely associated with $p27^{kip1}$ and demonstrate differential expression in the divergent clinical phenotypes seen in alternate flow and shear stress conditions.

Methods: A rabbit carotid artery interposition graft with jugular vein was placed and differential flow states were created through outflow branch ligation. Graft diameters and flow rates were documented at the time of implantation and harvest with ultrasound imaging. Vein grafts were harvested at 2 hours, 1 day, 7 days, and 28 days following implantation. Whole vessel homogenates were analyzed for gene expression using a custom Agilent rabbit microarray. Next, ingenuity pathway analysis (IPA) (Ingenuity, Redwood City, Calif) was employed to generate a list of the closest 150 upstream and downstream genes in relation to $p27^{kip1}$. This list was cross-referenced to the rabbit array list to identify overlapping genes, and this set of $p27^{kip1}$-associated genes was analyzed for divergent expression profiles between high and low shear conditions. These genes were then further explored using IPA for ontologic analysis and creation of signaling networks. dChip software (Harvard, Boston, Mass) was used for clustering analysis and heat map generation.

Results: Outflow branch ligation resulted in an immediate 90% reduction in flow on the ligated (low-flow) vein graft side compared with the high flow side (3.1 ± 0.4 vs 30.0 ± 2.2 mL/min), and a 15-fold difference in mean flow rates was observed throughout the 28-day perfusion period ($P < .001$). The reduction in flow led to a robust hyperplastic response, so that by 28 days a sevenfold increase in neointimal thickness was noted in the low-flow vs the high-flow vein grafts (231 ± 35 vs 36 ± 18 μm;

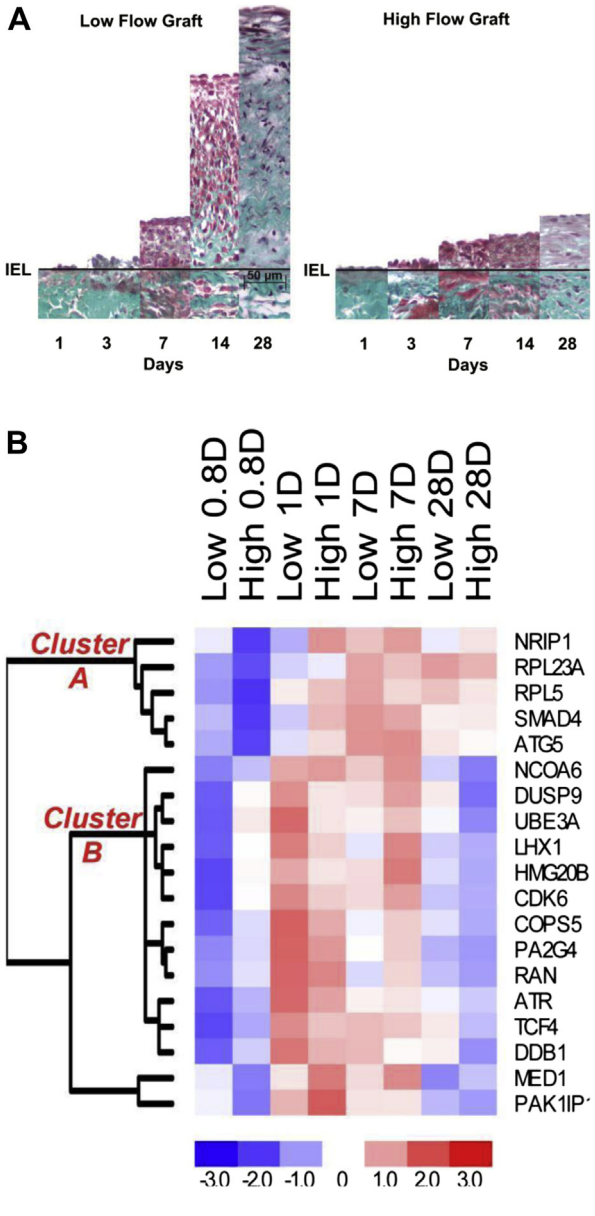

Fig 1.

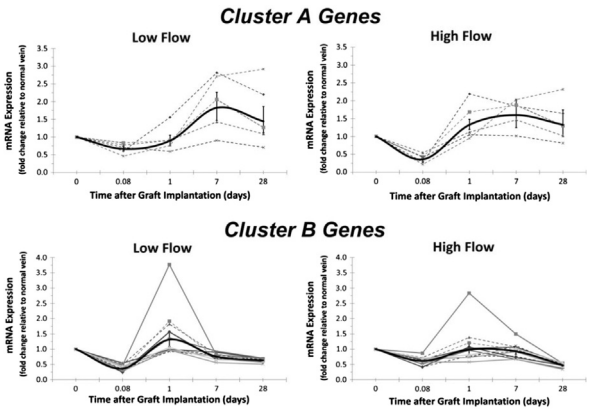

Fig 2.

$P = .001$) (Fig 1, *A*). IPA was used to identify the gene networks and signaling pathways surrounding $p27^{kip1}$. Nineteen probes sets within the microarray were identified to be components of the p27 network (Table). Sixteen of these genes encode nuclear proteins, the majority of which are transcription regulators. The top functions of this gene set are cell cycle regulation (13 genes), cellular growth and proliferation (17), gene expression (11), cellular development (14), and cell death and survival (12). A supervised clustering analysis of these genes revealed two primary patterns of gene expression, yielding two sets of genes with unique patterns of expression (Fig 1, *B*). Cluster A was characterized by a more delayed but prolonged upregulation compared with cluster B. Additionally, cluster B exhibits greater upregulation at 7 days, and greater downregulation at 28 days in the high-flow vs the low-flow grafts, suggesting a global flow-dependent genomic response (Fig 2).

Conclusions: Vein graft remodeling is a complex process driven by the interplay of local and systemic biology with mechanical forces. Despite technological advances and improvements in surgical techniques, the precise factors that determine whether a vein graft adopts an adaptive, outwardly remodeling phenotype, vs an occlusive phenotype, are largely unknown. A SNP of the $p27^{kip1}$ gene, a key cell-cycle regulator, has recently been associated with improved revascularization outcomes, yet the mechanisms underlying this clinical observation remain undefined. Here we attempt to dissect the gene pathways and networks at play in shaping these divergent outcomes. In the current analysis, we demonstrate that time-dependent response to injury following vein graft implantation exerts the dominant influence on alterations in the $p27^{kip1}$ regulatory network. Although changes in flow result in marked differences in graft phenotype, this biologic impact is mediated by a broad modulation of the $p27^{kip1}$ pathway. Difference in gene expression between high and low flow occurred predominately in the 1- to 4-week timeframe, the time at which robust proliferation is dominating the rapid growth of the intima. Intervention of the $p27^{kip1}$ pathway may offer an important option for modulating cell cycle processes that contribute to maladaptive vascular remodeling. In particular, cytoplasmic ribosomal and autophagy proteins appear to be the most promising candidates for therapeutic intervention.

Intentional Left Subclavian Artery Coverage During Thoracic Endovascular Aortic Repair (TEVAR) for Traumatic Aortic Injury: A Quality of Life Study

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Objectives: Thoracic endovascular aortic repair (TEVAR) is widely used for treatment of traumatic aortic injury (TAI). Stent graft coverage of the left subclavian artery (LSA) may be required in up to 40% of cases. We evaluated the long-term effects of intentional LSA coverage on symptoms and return to normal activity in TAI patients, compared with a similarly treated group without LSA coverage.

Methods: Patients were identified from a prospective institutional trauma registry between September 2005 and July 2012. TAI was confirmed using computed tomographic angiography. The electronic medical records, angiograms, and computed tomographic angiographies were reviewed in a retrospective fashion. Personal or telephone interviews were conducted using the SF-12v2 to assess quality of life. An additional questionnaire was used to assess specific LSA symptoms and the ability to return to normal activities. Data were analyzed by spearman rank correlation and multiple linear and logistic regression analysis with appropriate transformations (SAS software).

Results: During the study period, 82 patients (57 male, mean age 49.5 ± 20 years, mean ISS 34 ± 10.0) underwent TEVAR for treatment of TAI. Among them, 32 (39.5%) required left subclavian artery coverage (LSAC), while 50 had their LSA uncovered (LSAU). We found no statistically significant difference in SF-12 physical health scores ($\rho = -.08$; $P = .62$) between LSAC and LSAU patients. LSAC patients had slightly better mental health scores ($\rho = .62$; $P = .037$) than LSAU. LSAC patients did not have increased likelihood of experiencing pain ($\rho = -.0056$; $P = .97$), numbness ($\rho = -.12$; $P = .45$), parasthesia ($\rho = -.11$; $P = .48$), fatigue ($\rho = -.066$; $P = .69$), or cramping ($\rho = -.12$; $P = .45$). We found no difference in ability to return to activities between groups. The mean follow-up time was 3.35 years. Five (16%) of the LSAC patients expired during the follow-up period due to unrelated causes.

Conclusions: Intentional coverage of the LSA during TEVAR for TAI appears safe without compromising mental or physical health outcomes. Furthermore, LSAC does not increase the long-term risk of upper extremity symptoms or impairment of normal activities.

Table. $p27^{kip1}$ associated genes

Gene symbol	*Entrez gene name*	*Location*	*Function*
ATG5	autophagy related 5	Cytoplasm	Other
ATR	ataxia telangiectasia and Rad3 related	Nucleus	Kinase
CDK6	cyclin-dependent kinase 6	Nucleus	Kinase
COPS5	COP9 signalosome subunit 5	Nucleus	Transcription regulator
DDB1	damage-specific DNA binding protein 1	Nucleus	Other
DUSP9	dual specificity phosphatase 9	Nucleus	Phosphatase
HMG20B	high mobility group 20B	Nucleus	Transcription regulator
LHX1	LIM homeobox 1	Nucleus	Transcription regulator
MED1	mediator complex subunit 1	Nucleus	Transcription regulator
NCOA6	nuclear receptor coactivator 6	Nucleus	Transcription regulator
NRIP1	nuclear receptor interacting protein 1	Nucleus	Transcription regulator
PA2G4	proliferation-associated 2G4, 38kDa	Nucleus	Transcription regulator
PAK1IP1	PAK1 interacting protein 1	Nucleus	Other
RAN	RAN, member RAS oncogene family	Nucleus	Enzyme
RPL5	ribosomal protein L5	Cytoplasm	Other
RPL23A	ribosomal protein L23a	Cytoplasm	Other
SMAD4	SMAD family member 4	Nucleus	Transcription regulator
TCF4	transcription factor4	Nucleus	Transcription regulator
UBE3A	ubiquitin protein liqase E3A	Nucleus	Enzyme